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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional): H&U122

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

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Signature _____

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Application Number	Filed
10/525,558	September 2, 2005

First Named Inventor: Hacker

Art Unit	Examiner
1636	Joike, Michele K.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 35,843.
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

Signature

MARLANA TITUS
Typed or printed name

301-977-7227
Telephone number

JANUARY 17, 2011
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of 1 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of

Hacker et al. Group Art Unit: 1636

Application No. 10/525,558 Examiner: Michele Joike

Priority claimed from: PCT/EP2004/006886 (filed June 25, 2004) and German application 103 28 669.1 (filed June 26, 2003)

Filed: September 2, 2005

For: Plasmid-Free Clone of E. Coli Strain DSM6601

PRE-APPEAL BRIEF REQUEST FOR REVIEW

January 17, 2011

Hon. Commissioner of Patents
and Trademarks
PO Box 1450
Alexandria, VA 22313

Sir:

Responsive to the Office Action dated October 19, 2010, Applicant requests a pre-appeal brief request for review in the above-identified application.

The following is an identification of lack of prima facie case in the Examiner's rejection – failing to show proper motivation for making a modification in two obviousness rejections

There are two remaining obviousness rejections of the claims, both citing overlapping art. The four main references are (1) Uraji, (2) Blum-Oehler, (3) Trevors, and (4) Gasson. The Examiner cites Uraji for teaching a method to cure a single plasmid from a gram negative bacteria – not the DSM 6601 strain or any E. coli strain, or the pMut plasmids, or curing more than one plasmid. Blum-Oehler is cited for the disclosure of Nissle 1917 (DSM 6601), which is not plasmid-free but contains two plasmids (pMut1 and pMut2). The Examiner cites Trevors et al. for describing curing methods for removing bacterial plasmids. Alexeyev is cited for its description of a tetracycline resistance cassette in a plasmid. Gasson et al. is cited for teaching the curing of five plasmids from a Streptococcus strain.

The Examiner acknowledges that none of these references teaches a plasmid-free clone of DSM 6601 or even the desirability of acquiring such a clone.

"The Examiner agrees that none of the references individually teach the curing of the strain DSM 6601 or the desire to cure pMut1 and pMut2; that's why she used 4-5 references." (October 19, 2010 Office Action, page 4)

We respectfully submit that the Examiner has failed to present a prima facie case of obviousness because there is no motivation to modify the Blum-Oehler reference to acquire a clone that is free of both plasmids pMut1 and pMut2. No reference teaches the curing of DSM 6601. or the desire to cure it of both pMut1 and pMut2. Blum-Oehler represents the problem in the art solved by our plasmid-free strains – it presents absolutely no solution to its own problem.

The primary reference Uraji is itself quite irrelevant to our claims on many points, as is evident by the string of secondary references cited to make up for its deficiencies.

Uraji cures a non-E. coli strain (*Agrobacterium*) of a single plasmid via the introduction of the sacB gene; the second plasmid does not have sacB gene. In the October 19 Office Action at page 5, the Examiner argues that

"Uraji does not teach the introduction of two sacB genes, it only teaches the introduction of one sacB gene. . . . Knowing that sacB was used successfully by Uraji to cure the first plasmid, there is a reasonable expectation of success that that second plasmid could be cured."

The introduction of two sacB genes into the pMut1 and pMut2 plasmids is an affirmative requirement in our claims 2-6. Uraji, or any of the other cited references, does not teach or suggest the deliberate and separate introduction of two sacB genes, one into each of the pMut1 and pMut2 plasmids. Again, there is no motivation to cure both plasmids from DSM 6601. Uraji as a primary reference falls short to help establish a prima facie case of obviousness.

Further, Uraji teaches carefully that its curing techiques "should also be applicable to other types of plasmids in *Agrobacterium* groups". (See Abstract of Uraji et al.). From the standpoint of someone having ordinary skill in this art, *Agrobacterium* is neither genetically, physiologically or microecologically comparable to the probiotic,

non-pathogenic E. coli strain DSM 6601, which is used in humans to treat gastrointestinal dysfunctions and diseases. *Agrobacterium* can only infect and colonize plants; *E. coli* is a bacterium that populates the human and animal intestine. *Agrobacterium* and *E. coli* are two completely different organisms, and the removal or even desirability of removal of the plasmids would not be viewed by someone having ordinary skill in this art as being equivalent or even suggestive of each other. By their affirmative suggestion that their curing methods should be applicable to other types of plasmids in the *Agrobacterium* species, Uraji's own authors obviously are not suggesting to extrapolate their technique for use in curing plasmids in other bacterial species. Someone having ordinary skill in this art would likewise not have been reasonably expected Uraji's method to be useful for curing *E. coli* or other types of non-*Agrobacterium* species.

Trevors et al. is a review that describes several methods for "curing" bacteria from plasmids; however, none of these methods equate to the actual method the inventors used to construct their plasmid-free strains – which method required significantly more than mere routine procedures. As noted on page 2 of our application:

> It turned out in the exhaustive investigations that led to the present invention that plasmid-free clones of strain DSM 6601 cannot be prepared at all with normal genetic engineering methods or can be prepared only with great difficulty so that special paths must be taken in order to generate such clones. Since the wild type of the strain has two plasmids of different sizes in addition to its genomic DNA, the elimination of these plasmids must take place in several steps that take place in part in parallel.

The details of the special paths taken to generate our clones are provided in the text of our application, especially in the Examples. Specific details about the challenges overcome, blind alleys pursued, and the like, are not provided, so at first glance it may appear as if eliminating the pMUT1 and pMUT2 of E. coli strain DSM 6601 was merely routine. This is simply not the case. Please note that our disclosure strongly states that exhaustive investigations were undertaken to overcome the difficulties presented by elimination of the two plasmids of different sizes while preserving the genomic DNA of the E. coli (page 2, et seq). As would be understood by someone having ordinary skill in this art, the general methodologies described by Trevors would not have been useful to remove the two plasmids in E. coli strain DSM 6601. Trevors is only background

information, and does not provide the requisite motivation for modifying the Blum-Oehler strain.

The Gasson reference is cited for motivation to cure two or more plasmids, and even that reference deals with an entirely different strain (Streptococcus), and addresses a different problem, and solves its problem using a different curing process altogether. Gasson has been cited from a retrospective point of view – that is, to fill in a "gap" in the string of cited art, to show that a plasmid can be cured from a host. In Gasson's disclosure, a Streptococcus strain is cured of five plasmids. Curing strains of Streptococcus having a large complement of plasmids requires several obstacles to be overcome. Difficulties addressed by Gasson include the assignment of suspected plasmid-encoded phenotypes to individual molecules, the complicated analysis of plasmid transfer experiments, and the equally complicated analysis of the molecular study of individual plasmids from the complement (as also noted by the Examiner). The focus of the Gasson article is how to deal with these particular issues. The curing process itself is conducted as a protoplastic-promoted curing, which means that plasmid-loss occurs during the early stages of protoplast regeneration.

In the situation of the E. coli DSM 6601 of our invention, the pMut1 and pMut2 plasmids are both cryptic. There was no issue regarding which plasmid to cure. And of course, the method our inventors used for double-curing is completely different from the Gasson method. The method employed by Gasson is nearly irrelevant to the method our inventors adapted, and would not have been effective to identify or address the problem encountered by our method. The only parallel between our invention and Gasson is that a bacterial species is cured of more than one plasmid. However, the differences between our technology and Gasson's – different bacterial species, different problems encountered and overcome, different methods of curing – are simply too significant to be minimized or overlooked, which is what would be necessary to have this reference fill in the "gap" of the other cited art. For the purposes of our particular invention, Gasson would not have been a reference someone skilled in this art would have looked to for motivation or direction to cure DSM 6601 of the pMut1 and pMut2 plasmids.

In order to combine these references to make the current claims obvious, hindsight reconstruction is necessary using the applicants' own disclosure as a basis. The primary reference is too irrelevant, and the secondary references are too disconnected from our invention. It is impermissible to use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. (In re Fine, 837, F.2d 1071 (Fed. Cir. 1988); In re Fritch 972 F.2d 1260 (Fed. Cir. 1992). Using the inventor's success as evidence that one of ordinary skill in the art would have reasonably expected success represents an impermissible use of hindsight. Life Technologies, Inc. v. Clontech Laboratories, Inc., 224 F.3d 1320 (Fed. Cir. 2000).

CONCLUSION

There are clear deficiencies in the Examiner's prima facie case. The requisite motivation to combine the cited references is not present, unless hindsight reconstruction is liberally applied. A favorable decision is solicited.

Respectfully submitted,

Date: January 17, 2011

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